

Microwave irradiation synthesis of 3-(2-hydroxyalkyl)-2-methylquinazolin-4 (3H)-ones and their functionalization using the Mitsunobu reaction

Tarak Saïed ^{a,b}, Nourchaine Jelaiel ^a, Mohamed Lotfi Efrit ^{a*}
 Corinne Comoy ^b, Yves Fort ^b

^{a)} *Laboratoire de Synthèse Organique et Hétérocyclique, Département de Chimie
 Faculté des Sciences de Tunis, Université de Tunis El Manar, 2092-Tunis-Tunisie*

^{b)} *Structure et Réactivité des Systèmes Moléculaires Complexes
 Faculté des Sciences et Technologies, Université de Lorraine, France*

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Abstract: The synthesis of quinazolinones using a microwave method and their functionalization with the Mitsunobu reaction were investigated. The microwave method was proven to be rapid, simple and efficient in the synthesis of the starting quinazolinone. The results show an increase of obtained yields when compared with the conventional thermal method and the formation of the final derivatives in one step reaction without the activation of the alcohol function. The title quinazolinones were functionalized with a variety of variously substituted phenols using the Mitsunobu reaction to produce the corresponding new ether bridged derivatives in a 57-87% yield.

Keywords : Quinazolinone - Mitsunobu reaction - Microwave synthesis.

INTRODUCTION

The quinazolinone is a heterocyclic derivative of quinazoline which bears a carbonyl group. Among the quinazoline derivatives, the quinazolinone is one of the most biologically active compounds [1-4]. Indeed, it is used as anticonvulsants [5], anti-inflammatory [6], anti-leishmaniasis [7] or more typically as antimicrobial drugs [8]. Several strategies have been devoted to the synthesis and functionalization of the quinazolinone [9]. However, to the best of our knowledge the use of the microwave route was never proposed in these derivatives [10-12].

The first part of this work is devoted to a novel method for the synthesis of hydroxylated quinazolinones through a microwave method [13].

When compared to the conventional heating, the microwave method offers a time and material gain. The second part of this paper focuses on the use of the Mitsunobu reaction [14-15] for the functionalization of the synthetic hydroxylated quinazolinones, considering its ability to create ether bridges between two alcohol functions and the easy processing compared to the conventional synthetic methods in organic chemistry.

RESULT AND DISCUSSION

The functionalized N-aryliminoester was chosen as a precursor because it is well described in the literature [16] and widely used in the synthesis of heterocyclic compounds [17]. This substrate was mixed with three aminoalcohols which are:

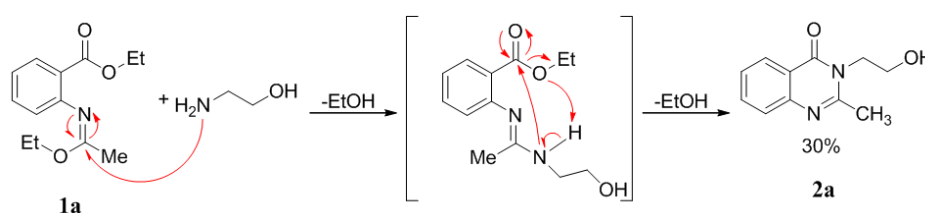
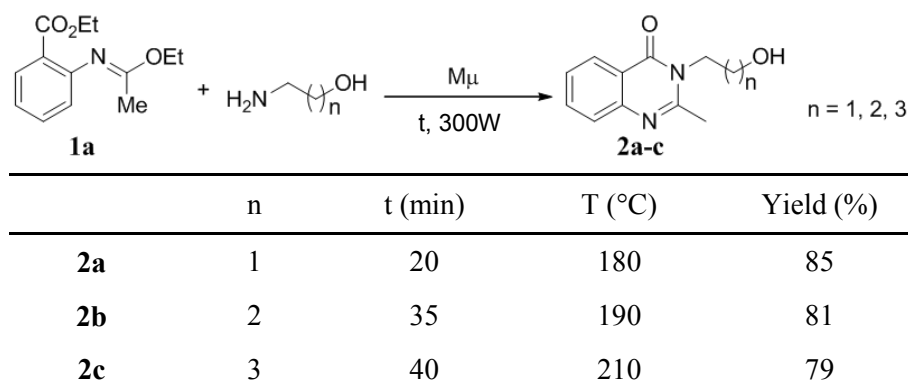


Figure 1: Preparation of hydroxyalkyl-quinazolines 2a.

* Corresponding author, e-mail address : medlotfi.efrit@gmail.com

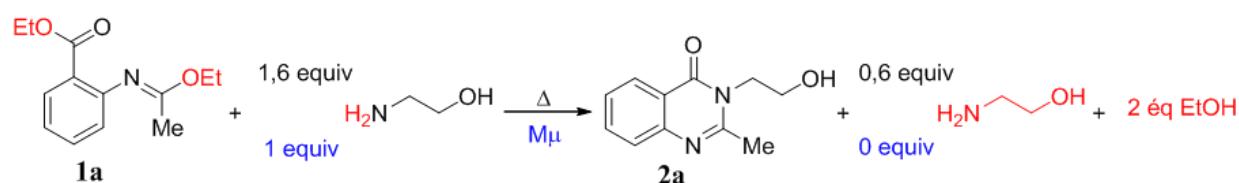
Table I: Synthesis of hydroxy-quinazolines **2a-c**.

the 2-aminoethanol, the 3-aminopropan-1-ol and the 4-aminobutan-1-ol in order to vary the length of the alkyl chain.

The first test was carried using the following conditions:

Ethyl acetimidate **1a** (1eq) and 2-aminoethanol (1.6 eq) in the presence of few drops of acetic acid as a catalyst, were stirred for 24 h at reflux in ethanol as solvent. The desired product **2a** was then obtained with a modest yield of 30% (figure 1).

The yield obtained using the conventional thermal method was about 30%, enabling the functionalization study of these compounds. The use of the microwave preparation method was suggested to enhance the yield of the quinazolines formation. The first test was carried in the presence of 1 equivalent of 2-aminoethanol for 20 min in the microwave reactor, without solvent and in the absence of catalyst. This leads to the formation of the quinazoline **2a** with a yield of 75%. The optimization

Table II: A comparison of the difference between the thermal and microwave methods for the synthesis of **2a**.

Method	Thermal method	Microwave method
Time	24 h	20 min
Equiv	1.6	1
Costs ^a	1505,6€	142,5€
Yield (%)	30	85
Energy	750 W	70 W
Catalyst	With	Without
Solvent	With	Without
E Factor	0.62	0.44
A E ^b	61%	70%
Secondary products	iminoester, aminoethanol, ethanol	Ethanol

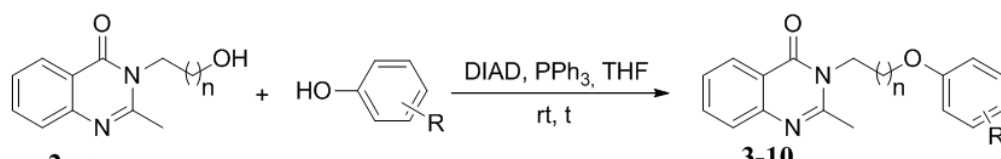
^a The costs of the products were taken from the Sigma Aldrich for 100 g, ^b (Atome Economy)

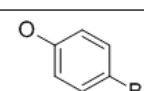
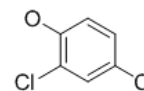
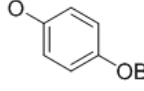
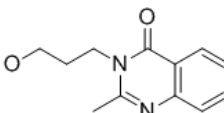
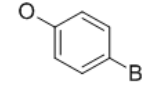
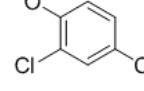
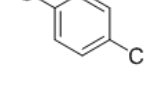
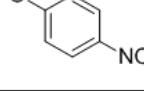
of the experimental conditions in the microwave reactor was performed on 0.3 mmol of iminoester **1a** using the open vessel mode. The quinazoline **2a** was obtained with an optimized yield of 86%.

The synthesis of the quinazolines **2b** and **2c** were carried out directly to the gram scale using 3-aminopropan-1-ol and 4-aminobutan-1-ol, respectively. The obtained results for the three hydroxylated quinazolinones are listed in Table I.

When comparing the two synthesis methods, one can deduce that the microwave method is more efficient than the thermal method economically and ecologically. The absence of catalyst and solvent as well as the reduction of the reaction time from 24 h to 20 min are the advantages for this method. We report in Table II a comparative study of different advantages and disadvantages of these two methods.

Table III: The results of the functionalization of the quinazolines **2a-c**.



Entry	Compound	N	Time	Phenol	Yield (%)
1	3	1	1 h		87
2	4	1	1 h		81
3	5	1	4 h		57
4	6	2	8 h		69
5	7	3	30 min		79
6	8	3	30 min		61
7	9	3	45 min		73
8	10	3	30 min		82

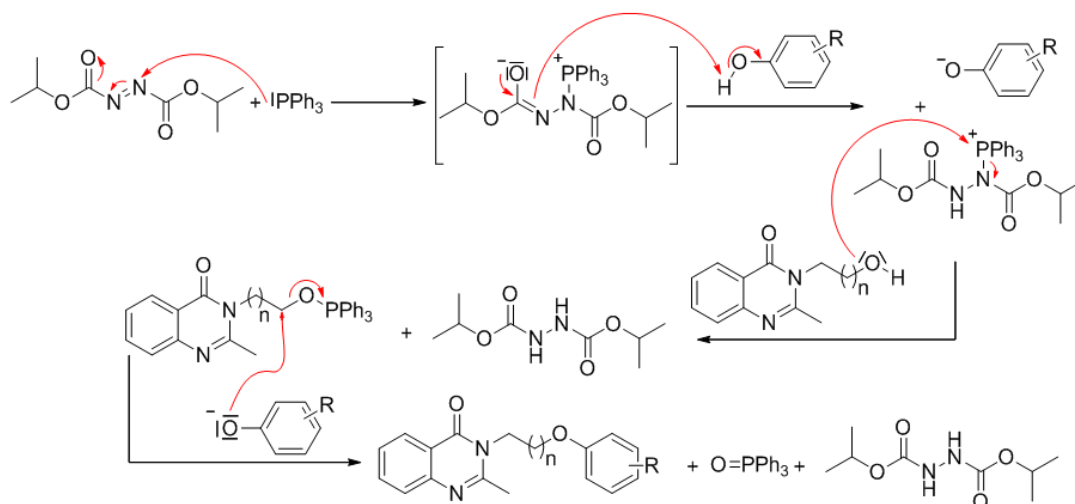


Figure 2: The possible mechanism of the functionalization of quinazolinones with the Mitsunobu reaction.

As can be observed, the microwave irradiations allow the cyclocondensation of iminoester **1a** under stoichiometric conditions and in a shorter time compared to the thermal conditions. This method can be proposed to a large number of alkyl chains with different lengths. On the other hand, the presence of the hydroxy group at the end of the chain allows the functionalization of this kind of molecules.

1. The Mitsunobu reaction as a functionalization tool

The particular structure of the hydroxylated quinazolinones and specially the presence of the hydroxy-alkyl chain on the quinazoline skeleton encouraged us to consider the Mitsunobu reaction as a functionalization method. The aim of this study is to access to more complex molecular structures which can be proposed to elicit a biological activity, depending on the graft pattern on the molecule.

Considering the success of the experiment described above, we applied the same preparation scheme to the other quinazolines of this family with various substituted phenols. The obtained results are shown in Table III.

Based on the obtained results listed in Table III, we can notice that the phenols showed great compatibility with the hydroxylated quinazolines **2a-c**. The reaction time depends upon the reagents and the length of the alkyl chain. Furthermore, the reaction shows a high tolerance to the halogens (Cl, Br). This protocol is promising with other

functional groups. Indeed, nitro or benzyloxy group can be introduced successfully with acceptable yields ranging from 57 to 82%. By using two equivalents of the product **7b** in the same conditions with a reaction time of 8 h, the synthesis of bis-quinazoline was achieved with a yield of 69%.

We proposed for this reaction, a mechanism containing three key steps of a "classic" Mitsunobu reaction between two alcohols in the presence of an azoic compound and an organophosphorus compound. In the studied reaction, the three steps are the formation of a zwitterionic adduct by reaction between triphenylphosphine and DIAD, the activation of the alcohol of the quinazoline by the formed zwitterionic species. Subsequently, the nucleophilic substitution between the activated alcohol *in-situ* and nucleophilic phenol leads to the formation of an ether bridge.

CONCLUSION

In this work, we have developed a new microwave method for the synthesis of hydroxylated quinazolinones. This method is faster and more ecological than the conventional thermal method. These quinazolinones were functionalized subsequently in a single step by the Mitsunobu reaction via a simple and effective method to give a series of ether bridged derivatives.

EXPERIMENTAL SECTION

Thermal route synthesis of quinazolinones:

The iminoester **1a** (0.03 mol, 7.05, 1 eq) was reacted with 2-aminoethanol (0.03, 3.05 g, 1.6 eq)

in the presence of 1 mL of acetic acid as a catalyst in 30 mL of ethanol. The reaction mixture was then stirred for 24 h under reflux and purified by column chromatography with 200 mL of ethyl acetate /cyclohexane (3/7). The product **2a** was obtained in a yield of 30%.

Microwave-assisted synthesis of quinazolinones:

The iminoesters **1a** (0.03 mol, 7.05, 1 eq) and 2-aminoethanol (0.05, 1.83 g, 1 eq) were reacted in a one pot without solvent and without catalyst. The reaction mixture was then stirred under microwave irradiation for 20 min and purified by washing with diethyl ether (30 mL). The product **2a** was obtained in a yield of 85%.

3-(2-Hydroxyethyl)-2-methylquinazolin-4(3H)-one **2a**.

Yield 85%. $^1\text{H NMR}$: δ = 2.64 (s, 3H, CH_3); 3.66 (q, 2H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $\text{CH}_2\text{-N}$); 4.12 (t, 2H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $\text{CH}_2\text{-O}$); 4.99 (t, 1H, OH); 7.42 (td, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 7.58 (d, 1H, $^3\text{J}_{\text{HH}} = 8\text{Hz}$); 7.77 (td, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 8.06 (dd, 1H, $^3\text{J}_{\text{HH}} = 8\text{Hz}$, $^4\text{J}_{\text{HH}} = 1\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 24.17, 47.39, 59.13, 120.81, 126.77 (2C), 127.17, 134.88, 147.92, 156.53, 161.94.

3-(3-Hydroxypropyl)-2-methylquinazolin-4(3H)-one **2b**.

Yield 81% $^1\text{H NMR}$: δ = 1.96 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 2.70 (s, CH_3); 3.49 (brs, 1H, OH); 3.63 (t, CH_2 , $\text{CH}_2\text{-N}$, $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 4.31 (t, 2H, $\text{CH}_2\text{-O}$, $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 7.47 (td, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 7.65 (d, 2H, $^3\text{J}_{\text{HH}} = 8\text{Hz}$); 7.76 (td, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 8.24 (dd, 1H, $^3\text{J}_{\text{HH}} = 8\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 23.12, 32.51, 40.25, 60.13, 122.44 (2C), 124.5, 124.9, 131.14, 146.43, 155.66, 162.01.

3-(4-Hydroxybutyl)-2-méthylquinazolin-4(3H)-one **2c**.

Yield 79% $^1\text{H NMR}$: δ = 1.69 (m, 2H, $\text{CH}_2\text{-CH}_2$, $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 1.90 (m, 2H, $\text{CH}_2\text{-CH}_2$, $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 2.67 (s, 3H, CH_3); 2.77 (brs, 1H, OH); 3.76 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 4.15 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 7.44 (t, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 7.63 (d, 2H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 7.73 (td, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 8.22 (d, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 23.31, 25.51, 28.47, 62.08, 120.68, 126.70, 126.83, 126.96, 134.51, 147.50, 154.34, 162.43.

General procedure for the functionalization of quinazolinones **2a-c**.

The hydroxyquinazoline **2a-c** (1eq), the triphenylphosphine (1.5 eq), the phenol derivative (1.5 eq) and the diisopropyl azodicarboxylate (1.5 eq) were mixed in two separate containers for 15 min in THF under argon atmosphere. The phenol/DIAD

mixture was then added dropwise to the first mixture at 0°C . The temperature was raised progressively to the room temperature during one hour and purified by washing with diethyl ether (30 mL).

3-(2-(4-Bromophenoxy)éthyl)-2-methylquinazolin-4(3H)-one **3**.

Yield 87%. F 137°C ; $^1\text{HNMR}$: δ = 2.60 (s, 3H, CH_3); 3.97 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 4.25 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 6.66 (dd, 2H, $^3\text{J}_{\text{HH}} = 9\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 7.19-7.41 (m, 3H); 7.56 (dd, 1H, $^3\text{J}_{\text{HH}} = 8\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 7.66 (m, 1H); 8.18 (dd, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 23.14, 42.11, 65.33, 113.26, 114.29, 116.19 (2C), 120.47, 126.50, 126.71 (2C), 132.37, 134.33, 147.29, 154.12, 157.56, 162.19.

3-(2-(2,4-Dichlorophenoxy)ethyl)-2-methylquinazolin-4(3H)-one **4**.

Yield 81%. F 121°C ; $^1\text{HNMR}$: δ = 2.92 (s, 3H, CH_3); 4.39 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 4.62 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 6.84 (d, 1H, $^3\text{J}_{\text{HH}} = 9\text{Hz}$); 7.14 (dd, 1H, $^3\text{J}_{\text{HH}} = 8\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 7.33 (d, 1H, $^3\text{J}_{\text{HH}} = 4\text{Hz}$); 7.45 (td, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$); 7.74 (m, 2H); 8.23 (dd, 1H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$, $^4\text{J}_{\text{HH}} = 2\text{Hz}$) $^{13}\text{CNMR}$: (CDCl_3) 23.96, 44.51, 66.82, 113.56, 120.32, 123.40, 126.39, 126.48, 126.54, 126.87, 127.66, 130.07, 134.49, 147.45, 152.63, 155.01, 162.33.

3-(2-(4-(Benzyloxy)phenoxy)ethyl)-2-methylquinazolin-4(3H)-one **5**.

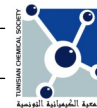
Yield 57%. F 232°C ; $^1\text{H NMR}$: δ = 2.73 (s, 3H, CH_3); 4.21 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 4.43 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 4.91 (s, 2H); 6.67 (m, 4H); 7.19-7.65 (m, 8H); 8.19 (d, 1H, $^3\text{J}_{\text{HH}} = 8\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 23.89, 44.66, 66.02, 70.65, 115.14, 115.91, 120.40, 126.63, 127.46, 128.40 (2C), 128.55 (2C), 128.64, 132.02 (2C), 132.21 (2C), 147.39, 152.48, 153.34, 154.98, 162.26.

3,3'-(Oxybis(propane-3,1-diyl))bis(2-methylquinazolin-4(3H)-one) **6**.

Yield 69%. F 266°C ; $^1\text{HNMR}$: δ = 1.17 (m, 4H, CH_2); 2.70 (s, 6H, CH_3); 3.53 (m, 2H); 4.21 (m, 2H, CH_2); 7.06-7.68 (m, 6H); 8.16 (d, 2H, $^3\text{J}_{\text{HH}} = 6\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 21.66, 21.71, 22.92, 23.23, 42.33, 43.04, 71.32, 72.43, 120.28, 126.56, 126.72, 128.38 (2C), 128.62, 131.99, 132.19 (2C), 147.36, 151.09, 151.56, 154.07, 154.64, 154.72, 162.14.

3-(4-(4-Bromophenoxy)butyl)-2-methylquinazolin-4(3H)-one **7**.

Yield 79%. F 199°C ; $^1\text{H NMR}$: δ = 1.92 (m, 4H, CH_2); 2.66 (s, 3H, CH_3); 4.01 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 4.17 (t, 2H, CH_2 , $^3\text{J}_{\text{HH}} = 6\text{Hz}$); 6.79 (d, 2H,



$^3J_{\text{HH}} = 8\text{Hz}$); 7.30-7.75 (m, 5H); 8.27 (d, 1H, $^3J_{\text{HH}} = 8\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 22.24, 26.85, 44.40, 67.72, 113.19, 116.53, 120.75, 126.99, 126.92, 128.67, 132.17, 132.22, 132.42, 132.54, 134.48, 147.54, 154.19, 158.18, 162.29.

3-(4-(2,4-Dichlorophenoxy)butyl)-2-methylquinazolin-4(3H)-one 8.

Yield 61%. F 178°C; $^1\text{H NMR}$: $\delta =$ 2.01 (m, 4H, CH_2); 2.70 (s, 3H, CH_3); 4.11 (t, 2H, CH_2 , $^3J_{\text{HH}} = 6\text{Hz}$); 4.25 (t, 2H, CH_2 , $^3J_{\text{HH}} = 6\text{Hz}$); 6.88 (d, 1H, $^3J_{\text{HH}} = 8\text{Hz}$); 7.17-7.78 (m, 5H); 8.29 (d, 1H, $^3J_{\text{HH}} = 8\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 23.42, 26.80, 44.04, 69.05, 114.35, 120.77, 123.98, 126.15 (2C), 126.68, 126.94, 127.02, 127.89, 130.29, 134.50, 147.57, 153.43, 154.29, 162.37.

3-(4-(4-Chlorophenoxy)butyl)-2-methylquinazolin-4(3H)-one 9.

Yield 73%. F 188°C; $^1\text{H NMR}$: $\delta =$ 1.80 (m, 4H, CH_2); 2.53 (s, 3H, CH_3); 3.88 (t, 2H, CH_2 , $^3J_{\text{HH}} = 6\text{Hz}$); 4.04 (t, 2H, CH_2 , $^3J_{\text{HH}} = 6\text{Hz}$); 6.63-7.64 (m, 7H); 8.15 (d, 1H, $^3J_{\text{HH}} = 8\text{Hz}$) $^{13}\text{C NMR}$: (CDCl_3) 22.78, 25.83, 43.89, 67.95, 113.24, 121.72, 123.98, 126.88 (2C), 126.97, 127.05, 127.56, 128.39, 131.09, 134.76, 147.88, 153.12, 154.33, 162.76.

2-Methyl-3-(4-(4-nitrophenoxy)butyl)quinazolin-4(3H)-one 10.

Yield 82%. F 163°C; $^1\text{H NMR}$: $\delta =$ 1.84 (m, 4H, CH_2); 2.57 (s, 3H, CH_3); 4.05 (t, 4H, CH_2 , $^3J_{\text{HH}} = 6\text{Hz}$); 6.84 (d, 2H, $^3J_{\text{HH}} = 8\text{Hz}$); 7.33-8.15 (m, 6H) $^{13}\text{CNMR}$: (CDCl_3) 23.42, 25.72, 44.08, 67.68, 114.67, 120.72, 126.19, 126.94 (2C), 126.94, 128.29, 127.56, 128.39, 134.56, 141.56, 147.22, 154.25, 162.25, 163.90.

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